INTRODUCTION

Psychiatric disorders are as old as mankind. As stress and strain increase day by day in the modern era, the frequency and severity of the psychiatric problems increase. The therapeutic agents, which are commonly used for the treatment of different psychiatric illnesses, are known as psychotropic agents. They are most appropriately used in the therapy of schizophrenia, the manic phase of bipolar (manic depressive) illness and other acute idiopathic psychotic illnesses or conditions marked by severe agitation. Effective antipsychotic agents include phenothiazines, structurally similar thioxanthenes, benzepines, butyrophenones (phenylbutylpiperidines) and diphenylbutylpiperidines. The other drugs used in manic depression in bipolar disorder are lithium carbonate or lithium citrate. Antipsychotic agents are also used to control acute or psychotic mania and prevent relapse. Anticonvulsant benzodiazepines are also used adjunctively. The other alternate or adjunctive treatment of mania include the anticonvulsants sodium valproate and carbamazepines. Virtually all antipsychotic drugs block dopamine receptors and reduce dopamine neurotransmission in forebrain. Antipsychotic agents of high potency tend to have more adverse extrapyramidal neurological effects, and low potency agents induce more sedative, depressive and autonomic side effects. Antipsychotic drugs are also classified as typical (or conventional) which causes extrapyramidal side effects (EPS) and atypical (or novel) drugs ameliorate EPS. Atypical and negative schizophrenia symptoms and do not cause EPS.
INTRODUCTION

Psychiatric disorders are as old as mankind. As stress and strain is increasing day by day in the modern era, the frequency and severity of the psychiatric problems increases. The therapeutic agents, which are commonly used for the treatment of the different psychotrophic illness, are known as psychotrophic agents. They are most appropriately used in the therapy of schizophrenia, the manic phase of bipolar (manic depressive) illness and other acute idiopathic psychotic illnesses or conditions marked by severe agitation. Effective antipsychotic agents include phenothiazines, structurally similar thioxanthenes, and benzepines; butyrophenones (phenybutylpiperidines) and diphenyl butylpiperidines; and indolones and other heterocyclic compounds. The other of drugs which are used for the treatment of mania and recoursance of mania and depression in bipolar disorder is lithium carbonate or lithium citrate. Antipsychotic agents are also used to control acute or psychotic mania and potent sedative anticonvulsant benzodiazepines are also used adjunctively. The other alternate or adjunctive treatment of mania include the anticonvulsants sodium valproate and carbamazepines. Virtually all antipsychotic drugs block D2-dopamine receptors and reduce dopamine neurotransmission in forebrain.

Antipsychotic agents of high potency tend to have more adverse extra pyramidal neurological effects, and low potency agents induce more sedative, hypotensive and autonomic side effects. Antipsychotic drugs are also classified as typical (or conventional) which causes extrapyramidal side effects (EPS) and produce antipsychotic effects, whereas atypical (or novel) drugs ameliorate both positive and negative schizophrenia symptoms and donot cause EPS.
In spite of considerable development in the field of antipsychotic agents there is no single drug available which could be considered as ideal since the currently available typical as well as atypical psychotropic agents (antipsychotic drugs) possess variable responses and various side effects. It is essentially require to discover better agents with less side effects.

Besides this, these compounds either possess nonanticonvulsive activity or are proconvulsants. Since epilepsy is very associated with psychiatric disorders, a drug with both antipsychotic as well as antiepileptic activity will be more beneficial. Search for better antipsychotic drug associated with antiepileptic properties with minimum side effects and maximum efficacy is the need of millenium.

The discovery of better antipsychotic drugs better than those available is mainly based on the synthesis of newer compounds in which the basic active nucleus has been incorporated in a new framework or appropriate pharmacophoric groups have been substituted in it with the aim to improve the efficacy with minimum side effects / risk benefit ratio. The work described in the present study is mainly based on this approach.

In the present work the following types of compounds have been synthesized and evaluated for their psychotropic activities.

**SERIES I**

- 3-Acetyl-5-chloroindole, 3-substitutedbenzyl-5-chloro ideneacetylidoles, 3-[2'-substitutedaryl-2, 3'-dihydro-1', 5'-benzothiazepine-4'-y1]-5-chloro indoles, 3-[2'-substitutedaryl-2', 3'-dihydro-1', 5'-benzothiazepine-4'-y1]-5-chloroindoles, 3'-[2'-substituedaryl-3'-substituedarylaminoethyleny-2', 3'-dihydro-1', 5'-benzothiazepine-4'-y1] 5'-chloro indoles and 3'[2'-substituedaryl-3'-substitued arylazo-2', 3'-dihydro-1', 5'-benzothia zepine-4'-y1] 5-chloro indoles.
SERIES II
2-Chloro-Phenothiazine, 2-chloro N-acetylphenothiazine, Z-chloro N-substitutedbenzylideneacetyl-phenothiazines, 2-chloro-[substitutedaryl-2,3-dihydro-[5-benzothiazepin-4-yl]phenothiazines and 2-chloro-N-[2-substitutedaryl-3-substitutedarylaminoethyl-2,3-dihydro-1,5-benzothiazepin-4-yl]phenothiazines and 2-chloro-N-[2-substitutedaryl-3-substitutedarylaminoethyl-2,3-dihydro-1,5-benzothiazepin-4-yl]phenothiazines.

SERIES III
7-Chloro-2-Methyl-1,5-benzothia/oxazepin-4(5H)-ones, 2-bromomethyl-7-chloro-1, 5-benzothia/oxazepin-4(5H)-ones, 7-chloro, 2-hydravinomethyl-1,5-benzothia/oxazepin-4(5H)-ones, 2-chloro, 2-substitubenzylidenehydravinomethyl-1, 5-benzothia/oxazepin-4(5H)-ones, 2-chloro-ones, 2-(4'-oxo-2'-substitutedphehythiazolidinyl)iminomethyl-1,5-benzothia/oxazepin-4(5H)-ones and 2-chloro-2-(4'oxo-3'-chloro-2'-substitutedphenyl-azetidinyl)-iminomethyl-1,5-benzothia/oxazepin-4 (5H)-ones.

SERIES I
3-[2'-substitutedaryl-2',3'-dihydro-1',5'-benzothiazepin-4'-yl]-5-chloroindoles, 3'[2'-substitutedaryl-3'-substitutedarylaminomethylene-2', 3'-dihydro-1',5'-benzothiazepin-4,yl5-chloro-indoles, 3-[2'-substitutedaryl-3'-substitutedarylazo-2',3'-dihydro-1',5'-benzotiazepin-4'-yl]5-chloroindoles.

Indole derivatives are important source of compounds of pharmacological interest as they have shown a wide spectrum of biological activities viz. anticonvulsant (Pojouhesh et al., 1999) and antipsychotic (Perregard & Perderson, 1992) activities. Furthermore substitution at third position of indole markedly enhances its antipsychotic profile. In addition, several
psychopharmacological activities in 1,5-Benzothia/oxazepine derivatives have also been reported. With a view to achieve better psychotropic activity, some new derivatives of benzothia/oxazepinyl indoles have been prepared and were screened for psychotropic activities.

3-Acetyl-5-chloro-indole on reaction with different aromatic aldehydes in the presence of 2% NaOH yielded 3-substituted benzylidene 5-chloro-indoles which on cyclization with 2-aminothiophenol in the presence of few drops of glacial acetic acid furnished 3-[2'-substitutedaryl-2',3'-dihydro-1',5'-benzothiazepin-4'-yl] 5-chloro-indoles (compounds 6-9). Compounds 6-9 underwent Mannich reaction with different substituted anilines afforded 3-[2'-substitutedaryl-3'-substituted arylaminomethylene-2',3'-dihydro-1',5'-benzothiazepin-4'-yl] 5-chloro-indoles (Compounds 10-17). On the other hand, compound 6-9 when reacted with different substitutedaryldiazonium salts in the presence of sodium acetate yielded 3-[2'-substitutedaryl-3'-substitutedarylazo-2',3'-dihydro-1',5'-benzothiazepin-4'-yl]5-chloro-indoles (Compounds 18-25). The purity of all the compounds have been checked by TLC. The structures were confirmed by IR, $^1$H NMR and mass spectroscopy.

All compounds were synthesized and were tested for their psychotropic activity as well as for acute toxicity studies. The most active compound of this series is compound 14 i.e. 3-[2'- (4''-N,N-dimethyl) aryl-3' arylaminomethylene-2',3'-dihydro-1',5'-benzothiazepin-4'-yl] 5-chloro-indole which was tested at the dose of 40 mg/kg i.p. and was found to be equal or more potent than the standard drugs for the all parameters of psychotropic activity except for cataleptic behaviour. ALD$_{50}$ of all the compounds was high, indicating a good safety margin.

**SERIES II**
2-Chloro-N-substitutedbenzyldeneacetylphenothiazines, 2-chloro-N-[2-substitutedaryl-2,3-dihydro-1,5-benzothiazepin-4-yl]phenothiazines, 2-chloro-N-[2-substitutedaryl-3-substitutedarylaminoethylen-2,3-dihydro-1,5-benzothiazepin-4-yl] phenothiazines

Phenothiazines constitute one of the most active class of compounds possessing diversified biological applications such as antipsychotic (Lin et al., 1996), anticonvulsant (Jaiswal et al., 1981) and anti-inflammatory (Bansal et al., 1999) activities. Literature survey reveals that various benzothiazepines (Campiani et al., 2000) as well as benzoazepines (Youssef & Said, 1997) have attracted considerable attention as they also have wide range of pharmaceutical activities. In light of these findings, synthesis of some novel phenothiazine derivate by incorporating different benzo/thio/oxazepines have been undertaken in order to assess their psychotropic profile.

The synthetic route of the compounds of this series started with the acetylation of 2-chloro-10H-phenothiazine to yield 2-chloro-N-acetylphenothiazine (compound 1), which on refluxing with various aromatic aldehydes in the presence of 2% NaOH yielded 2-chloro-N-substituted benzyldeneacetylphenothiazines (compounds 2-5). Compounds 2-5 underwent cyclization with 2-aminobenzenthiol in the presence of few drops of glacial acetic acid afforded 2-chloro-N-[2-substitutedaryl-2,3-dihydro-1,5-benzothiazepin-4-yl] phenothiazines (compounds 6-9) underwent Mannich's reaction with different aromatic anilines yielded 2-chloro-N-[2-substitutedaryl-3-substitutedarylaminoethylen-2,3-dihydro-1,5-benzothiazepin-4-yl] phenothiazines (compounds 10-25).

All the compound of this series were evaluated for their psychotropic as well as acute toxicity studies. All the compounds were tested at a dose of 40 mg/kg i.p.
Compound 18 i.e. 2-chloro-3-[2'-(4''-N,N-dimethyl)aryl-3'-arylaminomethylene-2',3'-dihydro-1',5'-benzothiazepin-4'-yl]phenothiazine, the most potent compound of this series, was tested at the three graded doses of 20, 40 & 80 mg/kg i.p. and was found to be equipotent or more potent than reference drugs for the amphetamine antagonism test, MES, PTZ, Rotarod and pole climbing tests. ALD₅₀ of all the newly synthesized compounds were found to be >1000 mg/kg p.o. except compound 4i, which has ALD₅₀>1600 mg/kg i.p. that indicated the good safety margin.

SERIES III

8-Chloro-2-Hydrazinomethyl-1, 5-benzothia/oxazepin-4 (5H)-ones, 8-chloro-2-substituted benzyldenehydrazinomethyl-1, 5-benzothia/oxazepin-4 (5H)-ones and 8-chloro-2-(4'-oxo-3'-chloro-1'-substitutedarylazetidinyl)-iminoethyl-1,5-benzothia/oxazepin-4 (5H)-ones

1,5-Benzothiazepine derivatives have gained much significant in recent years, due to its wide range of pharmacological applications like antidepressant (Diaz et al., 1996), CNS depressant (Grandolini et al., 1997), anticonvulsant (Diaz et al., 1994) and antipsychotic (Ligeois et al., 1994) applications. Furthermore, 1,5-Benzoxazepines were also found to possess psychotropic (Tatsuoka & Shibata, 1993) properties. Moreover, thiazolidinones have considerable importance as psychotropic agents (Takasugi & Saki, 1990) and azetidinones were also reported as biological active agents (Singh et al., 1997). These finding triggered particular interest to incorporate thiazolidinyl and azetidinyl moieties into 1,5-benzothia/oxazepine nucleus in a single molecular framework, with the hope to develop some promising clinically useful psychotropic agents.
8-Chloro-2-Methyl-1, 5-benzothia/oxazepin-4(5H)-ones were prepared which on bromination yielded 8-chloro-2-hydrazinomethyl-1,5-benzothia/ oxazepin-4 (5H)-ones. These schiff bases on cyclocondensation with thioglycolic acid and chloroacetylchloride furnished 8-chloro-2-(4'-oxo-2'-substitutedaryl- thiazoldinyl)-iminomethyl-1,5-benzothia/oxazepin-4(5H)-ones and 8-chloro-2- (4'-oxo-3'-chloro-2'-substitutedaryl-azetidinyl)iminomethyl-1,5-benzothia/ oxazepin-4 (5H)-ones respectively.

Purity of all the compounds were routinely checked by TLC. The structure of all the synthesized compounds were confirmed by elemental analysis (C,H,N), IR, 'H NMR and mass spectrometry. The spectral data of only representative compounds are given in experimental portion.

All the newly synthesized compound were tested for their psychotropic activities. The compounds of this series have shown mild to moderate response towards the all parameters of psychotropic activity. Compound 17 i.e. 8-chloro- 2-(4'-oxo-2'-N,N-dimethylaryl-thiazolidinyl)-iminomethyl-1,5- benzothiazepin-4 (5H)-one is the most active compound of this series, which posses highly significant results towards all parameters of psychotropic activity. Moreover, ALD₅₀ of all the compound was found to be quite high, suggesting a good safety margin.

Series IV

N-[2-substitutedaryl-isoaxazolin-4-yl]phenothiaazines,N-[2-substitutedaryl- 3-substitutedarylidine-isoaxazolin-4-yl]phenothiaazines,N-[2-substitutedaryl- 3-substitutedarylianiiniumethylene-isoaxazolin-4-yl]pheuothiazines.

Chlorpromazine , a phenothiazine derivative, is currently a useful drug for the treatment of various psychotropic disorders, gave the impetus to explore the
psychotropic activity of the phenothiazine derivatives. Heterocyclic/aliphatic variation at 10th position of phenothiazine nucleus remarkably increase the antipsychotic activity. Furthermore, different isoxazole derivatives were found to have good psychotropic activity. This has led us to synthesize new series of Isoxazolinyl phenothiazine to develop some newer more potent psychotropic agents.

Various N-[2-substitutedaryl-isoxazolin-4-yl]phenothiazines (3a-d) were synthesized by the reaction of N-substitutedbenzyldeneacetylphenothiazines with hydroxylamine hydrochloride in the presence of anhydrous NaOH. Further compound 4a-d underwent condensation with different aromatic aldehydes to afford N-[2-substitutedaryl-3-substitutedarylidene-isoxazolin-4-yl]phenothiazines (4a-h). On the other hand, when compound 4a-h underwent Mannich's reaction yielded N-[2-substitutedaryl-3-substitutedarylaminomethylene-isoxazolin-4-yl]phenothiazines (5a-h).

All the newly synthesized compounds were screened for psychotropic parameters like amphetamine antagonism, Induction of catalepsy, Rotarod performance, pentabarbitone sodium induced sleeping time and anticonvulsant (MES) activities at the dose of 40mg/kg i.p. and were found to exhibit mild to potent response towards these parameters. N-[2-(4'-N, N-dimethyl)aryl-3-(4"-N,N-dimethyl)arylidene-isoxazolin-4-yl]phenothiazine was the most potent compound of this series completely antagonised the stereotyped behaviour induced by amphetamine and did not show any catalepsy which reflects its good antipsychotic nature. ALD₅₀ of all the newly synthesized compounds were found to be >800 mg/kg p.o.